PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/000356	14.01.2005	19.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07K14/575, C07K14/705, A61K38/22

Applicant
MAX-PLANCK-GESELLSCHAFT ....

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/000356

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: BEYERMANN MICHAEL ET AL.; JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 275, no. 8, 25 February 2000 (2000-02-25), pages 5702-5709

1 Novelty (Art. 33(2) PCT)

The subject matter of the present application is a peptidic agonist of the corticotropin-releasing-factor-receptor-1 (CRFR1). This chimeric agonist is composed of peptide sequences at the N- and the C-terminus derived from sauvagine with a peptide derived from human/rodent corticotropin-releasing-factor (CRF) in between and an Alanine residue at position 40 leading to a peptide named "cortagine". Such a chimer composed of these two CRFs has not been disclosed before. Therefore, the subject matter of claims 1 to 14 is novel under Art. 33(2) PCT.

2 Inventive Step (Art. 33(3) PCT)

2.1 D1 is the closest prior art and discloses a chimeric CRF analogue composed of the N-terminus derived from ovine CRF or carp urotensin and the C-terminus derived from carp urotensin or frog sauvagine (see table 1).
From this the subject matter of the present application differs in that a different chimer is provided in which the middle part of the human/rodent CRF is flanked by the flanking parts of sauvagine.
The technical effect that is associated with said technical effect is the reduced immobility time, i.e. an improved antidepression-like activity and a higher selectivity for binding of CFRF1.
The technical problem to be solved is the provision of CFRF1 agonists with improved

antidepression-like activity.
This problem was known in the art. It was also known that chimeric agonists can be produced. However, the specific chimer shown in SEQ ID NO:1 has not been pointed to in the prior art. The skilled person was not directed to it in order to solve the problem posed. Therefore, the subject matter of claims 1 to 14 is inventive under Art. 33(3) PCT, as far as Glu21 is concerned.

2.2 The subject matter of claims 1 and 2 relates to peptides of a variable sequence (SEQ ID NO:1) in which six position are variable ((a) to (f)). Of these six, only the fifth position (e), i.e. amino acid 21 has been changed to Glu and was used for experimental verification of the technical effect which substantiates an inventive step (see point 2.1 above). It has not been verified whether the changes at the other amino acid positions will lead to the same technical effect, i.e. an improved antidepression-like activity and a higher selectivity for binding of CFRF1 in comparison to ovine CRF. If this is not the case for a specific variant, the problem to be solved would simply be the provision of a further CRF variant which would not be inventive in view of e.g. D1 as any chimer would be a mere selection from a number of equally likely alternatives from which the skilled person would choose in order to solve the problem posed.

3 Industrial Application (Art. 33(4) PCT)

The present claims fulfill the requirement of industrial applicability (Art. 33(4) PCT).

4 Clarity, Support, Disclosure (Art. 5, 6 PCT)

4.1 Terms like "highly selective" and "without having any significant cross-reactivity" used in claim 1 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject matter of said claims unclear (Art. 6 PCT). This is also true because said terms render the claims attempting to define the subject matter in terms of a result to be achieved.

4.2 The subject matter of claims 13 and 14 is speculative as a relation of the claimed compound to the diseases or conditions mentioned in said claims has not been shown in the application. Said claims are therefore not technically supported under Art. 6 PCT.
4.3 On e.g. page 1 of the description statements are made concerning the incorporation of publications. These general statements are not allowed as the patent specification should be self-contained (Guidelines 4.26).

Re Item VI
Certain documents cited

Certain published documents

TEZVAL HOSSEIN ET AL.; PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 101, no. 25, 22 June 2004 (2004-06-22), pages 9468-9473